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CASE REPORT

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Treatment of Depression with Vortioxetine in a Patient with Comorbid Major Depressive Disorder and Restless Legs Syndrome: A Case Report

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ABSTRACT

Many case reports have shown that the use of antidepressants can lead to restless legs syndrome (RLS). Vortioxetine is a new generation antidepressant with a multimodal mechanism of action on serotonin receptors. In this case report, partial improvement in RLS symptoms after treatment with vortioxetine in a patient with a co-diagnosis of major depressive disorder and restless legs syndrome will be discussed. A 59-year-old female patient was admitted to the psychiatry outpatient clinic due to depressive complaints for three months. In the control examination, it was learned that the patient had complaints of RLS that had been going on for about 20 years. RLS symptoms were increased with selective serotonin reuptake inhibitors (SSRI) used by the patient. In the follow-up examination in the first month after vortioxetine treatment, clinically significant improvement was observed in the patient's depressive complaints, while a partial reduction in RLS symptoms was observed.

Keywords: Antidepressant, dopamine, restless legs syndrome, vortioxetine

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INTRODUCTION

Restless Legs Syndrome (RLS) is a motor-sensory disorder characterized by unpleasant and painful sensations, particularly in the legs, and an irresistible urge to move them, felt during sleeping or at rest. Symptoms typically occur in the evening or at night, are relieved by movement, and often lead to sleep disturbance (1). RLS may develop in the presence of a number of medical conditions, including iron deficiency, end-stage renal disease, diabetes mellitus, rheumatic disorders, and multiple sclerosis (2). In addition, several antidepressants have been implicated in RLS, including mainly selective serotonin reuptake inhibitors (SSRIs) and mirtazapine (3,4). The dopaminergic system is believed to play a key role in the RLS development (5). It has been suggested that SSRIs induce RLS development by decreasing dopamine activity and increasing serotonin levels (6,7).

Vortioxetine is a new generation antidepressant with a multimodal mechanism of action. Vortioxetine is an inhibitor of serotonin (5-HT) transporter, an antagonist of 5-HT3, 5-HT7, and 5 HT1-D receptors, a partial agonist of 5-HT1-B, and a 5-HT1-A agonist (8). Moreover, in animal studies, vortioxetine has been demonstrated to increase serotonin, noradrenaline, dopamine, acetylcholine, and histamine levels in various brain parts (9).

In this case report, a 59-year-old female patient whose symptoms of RLS partially improved after starting treatment with vortioxetine for major depressive disorder will be presented.

Highlights

- **The dopaminergic system has an important role in the development of RLS.**
- **Antidepressants can cause HBS by reducing dopaminergic activity.**
- **Vortioxetine is a new generation antidepressant with a multimodal mechanism of action.**
- **Vortioxetine has been demonstrated to increase dopamine in the brain.**
- **Vortioxetine can be used to treat depression in co-diagnosis of MDD and HBS.**

CASE

A 59-year-old female patient (married, with two children, high school graduate, housewife) presented to the psychiatry clinic with complaints of low mood, loss of interest, lack of energy, anhedonia, and fatigue. She reported experiencing depression symptoms for three months, and this was the first time she presented to the psychiatric outpatient clinic. She was fully conscious, cooperative, and oriented on mental status examination. Her self-care was good, and her affect and mood were depressive. She had clear, comprehensible speech and harmonious

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association of ideas. Attention and memory were normal. She did not report perception deficits and hallucinations. Her thoughts contained feelings of hopelessness and worthlessness with no suicidal ideation. She scored 19 points on Hamilton Depression Rating Scale (HAM-D) which was administered to determine the severity of depression. She complained of weakness and fatigue, and laboratory assessments showed normal values for complete blood count, vitamin B12 and folate levels, liver function tests, ferritin level (36.5 ng/mL), renal function tests, and thyroid function tests. The patient has been receiving antihypertensive therapy (amlodipine besylate 5 mg/day) over the last two years. She was not receiving any other medications and did not have a history of comorbid conditions, alcohol use, or smoking. Based on these symptoms and findings, the patient was diagnosed with major depressive disorder. She was started on treatment with escitalopram 10 mg/day (with instruction to take 5 mg/day for the first five days) and asked to come back for a follow-up visit. She came back to the psychiatric outpatient clinic ten days later, complaining about pain in her legs that she experienced after going to bed every day, which started on the first day of treatment. She reported that her leg pain disappeared during the day and only occurred at night after going to bed. She stated that the severe pain in her legs was relieved when she moved her legs, and only then she could fall asleep. Thus, the patient fulfilled all four criteria for RLS established by the International Restless Legs Syndrome Study Group (IRLSSG) (10). The International Restless Legs Scale (IRLS), developed by the IRLSSG to assess the disease severity, was administered to the patient. The IRLS consists of ten questions, each assigned a score of 0 to 4. The total score indicates the severity of the disease, which is rated as follows: 1 to 10 points, mild; 11 to 20 points, moderate; 21 to 30 points, severe; and 31 to 40 points, very severe (11). Our patient scored 29 points on IRLS and therefore was considered to have severe RLS. She reported having similar complaints 2-3 days a week for nearly 20 years on detailed history. She stated that her son and mother had the same complaints so she never sought medical help for her complaints, thinking that this was a familial condition that she did not regard as a disease. Prior to starting escitalopram therapy, she had experienced moderate leg pain 2-3 days a week at night, which was almost completely relieved by moving her legs. The patient had mild sleep disturbance and mild daytime fatigue due to her complaints. She considered that this was affecting her mental state and daily activities. Thus, she had moderate RLS (13 points) based on her complaints before antidepressant therapy was initiated. It was learned from her history that citalopram treatment was recommended by a doctor whom she consulted for headache complaint about a year ago, and her RLS symptoms worsened when she started taking citalopram and resolved upon discontinuation of the drug. The patient's current condition and laboratory investigations were normal, and she had no underlying condition that could cause secondary RLS. Her family history was positive for RLS. Accordingly, she was diagnosed with primary RLS.

In our patient, RLS symptoms worsened by the use of SSRI antidepressants. At that time, she had persistent depressive symptoms and scored 21 points on HAM-D scale. She was started on vortioxetine 10 mg/day. On the follow-up examination one month later, significant clinical improvement was observed in her depression symptoms and her HAM-D score was four. The patient reported that the frequency (once or twice a week) and severity of her RLS symptoms decreased compared to previous years. She scored 8 points on the RLS disease severity scale (mild RLS). She was advised to continue treatment with vortioxetine 10 mg/day. The psychiatric assessment of the patient at three months was normal. She scored 4 points on HAM-D and 8 points on IRLS. The patient was informed that there is no literature on the partial improvement of RLS symptoms after vortioxetine treatment, and written informed consent was obtained from her to publish her case.

DISCUSSION

In our case, family history was positive for RLS, and no laboratory abnormalities which could be associated with RLS were detected at the time of initial presentation. Moreover, the patient did not have any medical condition that could be suggestive of secondary RLS. She has been receiving antihypertensive treatment for two years, but her RLS symptoms persisted at the same severity level for nearly twenty years. She has not been receiving any other medication, and therefore, drug-induced RLS was excluded. Ultimately, she was diagnosed with primary RLS. In our case, there was a significant increase in RLS symptoms with the use of antidepressants, both of which were SSRIs (citalopram and escitalopram). In the literature, there are many case reports of restless legs syndrome induced by SSRIs (12). However, a recent study did not find a link between antidepressant use and RLS development (13). Decreased dopaminergic activity is believed to play a key role in RLS development. RLS symptoms ameliorate with low-dose dopamine agonists (5). It is considered that SSRIs cause RLS symptoms by inducing an increase in serotonergic activity and a decrease in dopaminergic activity (6,7).

With its multiple pharmacological modes of action, vortioxetine acts as a serotonin (5-HT) transporter inhibitor, a 5-HT3, 5-HT7, and 5HT1-D receptor antagonist, a 5-HT1-B partial agonist, and a 5-HT1-A agonist (8). Additionally, animal studies have demonstrated that vortioxetine increases serotonin, noradrenaline, dopamine, acetylcholine, and histamine in different parts of the brain (9). Enhanced release of dopamine in the brain by vortioxetine demonstrated in vivo may explain the improvement of RLS symptoms in our patient. On the other hand, mirtazapine, which has been shown to induce RLS in several case reports, has a high affinity for histamine 1 receptor and strongly blocks this type of receptors (3,14). In addition, it is known that antihistamines may also cause RLS (1). For these reasons, the partial improvement of RLS symptoms in our patient may be associated with increased histamine levels in the brain by vortioxetine, as demonstrated by animal studies. At the same time, marked improvement in depression symptoms following vortioxetine treatment as observed in our patient may have led to a reduction in her RLS symptoms. However, when we reviewed her history, she has never sought psychiatric help before, and experienced depression symptoms for the last three months. Additionally, our patient had RLS symptoms for quite a long time and has a family history of RLS. Taking into account all of these considerations, it was concluded that RLS symptoms of our patient were not associated with major depressive disorder.

It is not possible to present definitive evidence that vortioxetine improves RLS symptoms based on our case report. There is no literature data to support such a conclusion. Nevertheless, our case report suggests that vortioxetine can be a safe therapeutic option in the treatment of depression symptoms in patients with major depressive disorder presenting with RLS. Prospective studies examining the possible relationship between antidepressants and RLS are warranted.

Informed Consent: Written informed consent was obtained.

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